BETA BLOCKERS INHIBIT ADRENERGIC RESPONSES MEDIATED THROUGH THE BETA RECEPTORS
Propranolol introduced in 1963 was the first betablocker. Since then drugs of this class have proliferated and diversified.

**Mechanism of action**
1. Reduction of adrenergic response mediated via β receptors.
2. Inhibition of renin release.
3. Inhibition of central nervous sympathetic outflow, thereby inducing presynaptic blockade which in turn reduces the release of catecholamines.
4. Reduction of venous return and plasma volume

**Classification of beta blockers**
1. Solubility based
   a. Hydrophilic (atenolol, carvidilol, nebivolol)
   b. Lipophilic—highly soluble (prapranolol), moderately soluble (metaprolol and labetalol)
2. Selectivity based
   a. Nonselective (β1 and β2)
      1. Without intrinsic sympathomimetic activity - propranolol, sotalol, timolol
      2. With intrinsic sympathomimetic activity- pindolol
   b. Cardioselective (β1) metaprolol, atenolol, acebutolol, bisoprolol, esmolol, betaxolol, celiprolol, nebivolol

**Time research based classification**
1. First generation (older, nonselective)-propranolol, sotalol, timolol, pindolol
2. Second generation (β1 selective)-metaprolol, atenolol, acebutolol, bisoprolol, esmolol
3. Third generation (additional α blocking property and vasodilator property)- labetolol, carvidilol, celiprolol, nebivolol

**Need for improved beta blockers**

**Adverse effects of older agents**
1. Bronchoconstriction.
2. Deliterious effects on lipid profile and insulin sensitivity.
4. No significant blood pressure control.

**Third generation beta blockers** (Carvedilol, Labetolol, Nebivolol)

**Labetolol**
1. Nonselective beta blocker.
2. But has additional α blocking activity.
3. No significant effect on heart rate and cardiac output.
4. Specific use in pheochromocytoma and PIH.
5. Available in injectable form so widely used in management of hypertensive emergencies.
6. But increase incidence of respiratory distress syndrome, sepsis and seizures in infants of labetolol treated PIH.

**Carvedilol**
1. Non selectve beta blocker.
2. Additional α blocking activity.
3. Limited effects on heart rate and cardiac contractility.
4. Used in LV dysfunction following MI.
5. Chronic primary HTN.
6. Useful in portal hypertension due to reduction in hepatic venous pressure gradient.
7. Vascular insulin sensitivity is preserved.
8. Increased coronary flow reserve and improved endothelial function.

**Table 1: Comparison of Conventional and Newer Beta Blockers**

<table>
<thead>
<tr>
<th>Effects</th>
<th>Conventional</th>
<th>Newer</th>
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<tbody>
<tr>
<td>Bronchoconstriction</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Dysidemia, diabetes</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Primary prevention of CV risk</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Core BP/ MAP reduction</td>
<td>+</td>
<td>-</td>
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</tbody>
</table>
9. Lowering LV mass index and LVH (as compared to metolor).
10. Better glycemic effect/metabolic effect in diabetics as compared to metolor, best in both white and female sub group.(metolor increased HbA1c levels in all groups except non white and no black)
11. Added therapy with carvedilol in diabetic patients has shown reduced TG, total cholesterol and microalbuminuria.

**Nebivolol**
1. Highly selective β1 blockers.
2. Also acts as a NO donor from endothelium (due to stimulation of endothelial NO synthase) produces vasodilatation.
3. Improve endothelial function.
4. Anti oxidant property (directly reacts with free radicals scavenging reactive oxygen species).
5. Effective lowering of central aortic pressure and MAP than atenolol(both equally effective in lowering brachial pulse pressure and aortic stiffness).
6. Provides relief in intermittent claudication.
7. Significantly lowers sitting BP (SBP and DBP in mild to moderate HTN).
8. Single dose(5-20mg) therapy so compliance is better.
9. Specifically used in older patients(> 62yrs) as this age group tends to have more systolic blood pressure
10. Besides monotherapy, very effective in combination with diuretic,CCB and other antihypertensives.
11. Favourable adverse effect profile.
12. Evening dosing significantly lowers day time, night time and 24 hr BP and prewaking SBP called morning surge.
13. In prehypertensives also significantly reduces central aortic systolic,diastolic BP and MAP
14. Significantly increases urinary nitrite and nitrate excretion(indication of increased NO production).
15. PROBE trial showed better decrease in LV mass and mass index by nebivolol group as compared to Ramipril group
16. Nebivolol equally effective in reducing peripheral BP and augmentation index like quinapril and aliskerin.
17. equally effective as valsartan in hypertensive patients with obstructive sleep apnea with advantage of reducing heart rate.

Newer β blockers nebivolol,carvdiolol have comparable efficacy with CCB and ACEI/ARB with regards to control of hypertension and reduction of cardiovascular risk.

Still more clinical trials are required to have better understanding regarding these agents.

**REFERENCES**